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A long noncoding RNA lincRNA EPS expression level in renal anemia in chronic kidney disease

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Abstract

Aim: Chronic Kidney Disease (CKD) is a long-term medical condition characterized by the gradual loss of kidney function over time. Anemia is one of the most important causes of morbidity in patients with CKD. Anemia negatively affects the quality of life and mortality of patients and increases the progression of kidney disease. This is the first study to indicate lincRNA_EPS expression levels in CKD patients with renal anemia.

Material and Methods: A total of 59 people were included in this study with 40 patients and 19 control groups. Analyzes of lncRNA expression levels were performed by RT-qPCR method. Total RNA (including miRNA and lncRNA) was obtained from serum and plasma using an RNA isolation kit. Then, RNA concentration and purity were determined spectrophotometrically. The integrity of total RNA was determined by agarose gel electrophoresis.

Results: This study concluded that the lincRNA-EPS expression values were found to be significantly higher in the CKD group. There was no statistically significant correlation between the eGFR level of the patients and the lincRNA-EPS expression levels. However, a statistically significant positive correlation was found between eGFR values and hemoglobin levels in the patient group.

Discussion: Considering the increased lincRNA-EPS expression level in CKD patients with renal anemia and its inverse correlation with EPO usage, a potential mechanism for facilitating erythropoiesis may involve both elevated lincRNA-EPS expression and suppression of the pro-apoptotic gene Pycard. Larger and more clinical studies are needed to fully elucidate the mechanism of action of the renal anemia-EPOlincRNA-EPS relationship. In the light of these studies, it will be possible to identify new factors that play a role in the formation mechanisms of renal anemia and to evaluate new treatment alternatives.

Keywords

Chronic Kidney Disease, Renal Anemia, Erythropoietin, Long Non-Coding RNA, lincRNA_EPS

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This study was approved by the Ethics Committee of Hatay Mustafa Kemal University Clinical Research (Date: 2021-04-08, No: 2021/39)

Introduction

Chronic Kidney Disease (CKD) is a very common clinical entity with an irreversible, progressive and high cardiovascular risk secondary to changes in the function and/or structure of the kidney due to many reasons. CKD is an independent risk factor for cognitive dysfunction, hospitalization, and all-cause mortality [1-3]. CKD is very common in the general adult population and it is estimated to increase over time and reach a percentage of 13.1% among adults in the United State [4]. Oxidative stress (OS) plays a significant role in the pathogenesis and progression of CKD. CKD is associated with increased production of reactive oxygen species (ROS) within the kidney. Various factors contribute to this, including inflammation, ischemia-reperfusion injury, mitochondrial dysfunction, and the activation of the renin-angiotensin-aldosterone system (RAAS). These ROS can damage cellular components such as lipids, proteins, and DNA leading to kidney injury and dysfunction [5-7]. OS can directly damage red blood cells, making them more susceptible to premature destruction (hemolysis). This process reduces the lifespan of red blood cells and contributes to anemia by decreasing the total number of functional red blood cells in circulation. Numerous studies indicate that OS is a pivotal role in the development of several diseases [8-14].

Anemia is a common complication of CKD and causes poor quality of life in patients with CKD. Although the mechanisms involved in the pathogenesis of renal anemia include chronic inflammation, iron deficiency, and shortening of the half-life of erythrocytes, the primary cause is relative erythropoietin deficiency. The American National Kidney Foundation Kidney Early Assessment Program has shown that the risk of anemia increases significantly when the glomerular filtration rate falls below 60 mL/min/1.73 m2 [16]. The gene encoding human erythropoietin (EPO) is located on chromosome 7 and covers about 3,000 base pairs. It contains 5 exons and 4 introns and encodes a 193 amino acid polypeptide [17]. Circulating EPO is mainly produced by peritubular fibroblast-like interstitial cells of the kidney [18]. EPO is considered an important growth factor for late erythroid progenitor cells. Activation of EPO receptors on physiologically immature erythroid cells produces an intracellular signal that ensures the survival of these cells. The expected compensatory response to anemia is a high rate of erythropoiesis with an inverse ratio between hormone concentration and Hb concentration [19]. Although chronic renal failure anemia is a complex disease in which many factors may play a role, the main defect is absolute or relative EPO deficiency. In most patients with substantially impaired renal function, EPO production is impaired at any hematocrit concentration independent of the level. The relative proportion of non-coding genomic DNA increases with developmental complexity, suggesting that ncRNAs served increasingly important biological functions during eukaryotic evolution. lncRNAs have come to the fore with newly defined roles in a wide variety of biological processes, including cell division, survival and differentiation [20]. The expression pattern of lncRNA genes has been shown to be much more tissue and cell type specific than for protein-coding genes [21]. LincRNA-EPS is minimally expressed in other hematopoietic lineages, it indicates erythroid specificity. In this study, the expression levels of a specific lncRNA (lincRNA-EPS) were examined in patients with CKD-related renal anemia and this lncRNA level was compared with a healthy control group. The relationship between this identified lncRNA (lincRNA-EPS) and anemia parameters is studied for the first time in humans. In the analysis of the results, if a significant relationship is shown between the determined lncRNAs and anemia parameters, it is aimed to determine new factors that play a role in the pathophysiology of renal anemia and to evaluate new treatment alternatives.

LincRNA-EPS (one of the non-coding RNA family) was identified as a lincRNA that facilitates erythropoiesis by suppressing apoptosis via reducing the expression of the proapoptotic gene Pycard without altering erythroid differentiation.(22). It is therefore important to determine how lincRNA-EPS represses Pycard and perhaps other proapoptotic targets. The most likely mechanism appears to be that lincRNA-EPS indirectly represses Pycard by inducing the synthesis of transcriptional repressors (23).

Material and Methods

Study Groups

A total of 59 people were included in this study with 40 patients and 19 control groups. The inclusion criteria of study: Patients over 18 years of age, patients with stage 3-5 CKD and hemoglobin <10 g/dl, EPO-naive or EPO-using patients; the exclusion criteria of study: Patients on hemodialysis or peritoneal dialysis, who have had a kidney transplant, with active infections, with known malignancy, have chronic liver disease, gastrointestinal bleeding, or other active bleeding conditions and the pregnant or breastfeeding women.

This study was conducted on patients with stage 3-5 CKD and hemoglobin value below 10 g/dL, who applied to Nephrology outpatient clinic of Hatay Mustafa Kemal University Training and Research Hospital between August 2021 and April 2022.

Sample acquisition

Peripheral blood samples from chronic kidney patients and healthy controls were taken into tubes without and with anticoagulant (EDTA) (biochemistry tube with gel). After the blood samples taken into the biochemistry tube were coagulated at room temperature (20-30 minutes), they were centrifuged at 3500 rpm for 10 minutes + 4 °C to obtain serum. Serum samples were stored at -80 degrees until the day of study. The blood samples taken into the tube containing the anticoagulant were centrifuged at 3500 rpm for 10 minutes + 4 °C in the same way, and the plasma part was transferred to a separate microcentrifuge tube. These samples were also stored at –80 °C until analysis.

Gene Expression Analyzes

Analyzes of lncRNA expression levels were performed by RT-qPCR method. Total RNA (including miRNA and lncRNA) was obtained from serum and plasma using an RNA isolation kit. Then, RNA concentration and purity were determined spectrophotometrically. The integrity of total RNA was determined by agarose gel electrophoresis. RNA samples with A260/A280 ratio between 1.8-2.0 were converted into cDNA using the cDNA synthesis kit. Real Time Quantitative Polymerase chain reaction (RT-qPCR) analyzes were performed on RotorGene device using SYBR Green master mix kit.

Primers associated with target genes were obtained from the manufacturer. LncRNA (lincRNA-EPS) gene expression analyzes were performed using primers. Analysis of gene expression data was done with QIAGEN's online program Data Analysis Center-RT2 Primer Assay. In the calculation of P values, the transcript was calculated based on 2-ΔΔct values for each gene in the control and treatment groups, and p values below 0.05 were considered significant. GAPDH, β-actin and U6' were used as housekeeping genes in normalization.

Statistical analysis

Statistical analysis was performed by Statistical Package for the Social Sciences (SPSS) 26 (SPSS Inc., Chicago, IL, USA) software. The collected data were calculated with appropriate descriptive statistics (mean, median, ratio, standard deviation, 95% confidence interval, etc.) methods. The conformity of the study data to the normal distribution was determined by the Shapiro-Wilk test. A comparison of data that did not show normal distribution was performed with the Mann-Whitney U test. P values less than 0.05 were considered significant. Spearman rank correlation was used because the data did not show normal distribution in the correlation analysis of the parameters. Results were expressed as mean ± standard deviation or median ± 25-75% percentile values ('interquartile range', IQ). 'SPSS 26' computer program was used for statistical analysis.

Ethical Approval

This study was approved by the Ethics Committee of Hatay Mustafa Kemal University Clinical Research Ethics Committee (Date: 2021-04-08, No: 2021/39).

Results

This study consists of 59 people in total, 40 of whom are from the patient group and 19 from the healthy subjects. Demographic characteristics, revealing minimal similarities between the patient and control groups are shown in Table 1. Females comprised 75.0% (30) and 52.6% (10) of the patient and control groups, respectively, while males constituted 25.0% (10) and 47.4% (9). Patients had a mean age of 64 ± 12 years, whereas the control group's mean age was 59 ± 9 years. Notably, body mass index, smoking, and blood pressures exhibited comparability between the two groups. As additional disease to CKD in the patient group: Isolated hypertension in 11 (27.5%) patients, hypertension, diabetes, hypertension and coronary artery disease in 9 (22.5%) patients, diabetes, hypertension and hyperlipidemia in 8 (20.0%) patients, diabetes and hypertension in 5 (%12,5) patients, coronary artery disease and hypertension in 4 (%10,0) patients, hyperlipidemia and hypertension in 2 (5.0%) and 1 patient has a diagnosis of isolated diabetes (Figure 1). In the patient group; 17 (42.5%) patients with an eGFR value of 30-59 ml/min/1.73m2 were evaluated as stage 3, 16 (40.0%) patients with an eGFR value of 15-29 ml/min/1.73m2 as stage 4, 7 (17.5%) patients with eGFR <15 ml/min/1.73m2 as stage 5 CKD.

The patients classified as stage 3 CKD, 9 (52.9%) hypertension and diabetes, 7 (41.1%) hypertension, 1 (6%) diabetes; the patients classified as stage 4 CKD, 11 (68.75%) hypertension and diabetes, 5 (31.25%) hypertension; the patients classified as stage 5 CKD, 5 (71.42%) hypertension, 2 (28.58%) hypertension and diabetes were the causes of kidney disease (Table 2). The distribution of EPO usage was 4 (23.52%) in stage 3 CKD patients, 5 (31.25%) in stage 4 CKD patients and 6 (85.71%) in stage 5 CKD patients. EPO usage doses in CKD patients according to stages were calculated as 50 mcg/week in stage 3 CKD patients, 46 mcg/week in stage 4 CKD patients, and 48.33mcg/week in stage 5 CKD patients (Table 2).

The laboratory values of all patients included in the study, the

Table 1. Demographic characteristics and mean blood pressure values of the patients

	Total (n=59) (Mean±SD)	Patient (n=40) (Mean±SD)	Control (n=19) (Mean±SD)	p
BMI (kg/m²)	28.86 ±4.03	28.31 ±4.27	30.03 ±3.30	0.069
Smoking	Yes (%): 17 (28.8)	Yes (%): 12 (30.0)	Yes (%): 5 (26.3)	0.772
	No (%): 42 (71.2)	No (%): 28 (70.0)	No (%):14 (73.7)	
Systolic Blood Pressure (Mean±SD) (mmHg)	129.58 ± 14.15	131.50 ± 16.41	125.53 ± 5.98	0.188
Diastolic Blood Pressure (mean±sd) (mmHg)	75.85 ± 4.03	75.50 ± 9.39	76.58 ± 7.08	0.444

BMI: Body Mass Index

Table 2. Causes of Patients' Kidney Disease and EPO Doses

	CKD Stage 3 Number (Percent)	CKD Stage 4 Number (Percent)	CKD Stage 5 Number (Percent)
Kidney Disease Causes	HT: 7 (%41,1)	HT: 5 (%31,25)	HT: 5 (%71,42)
	DM: 1 (%6)	HT and DM: 11 (%68,75)	HT and DM: 2 (%28,58)
	HT and DM: 9 (%52,9)		
EPO Usage (Darbepoetin Alfa)	40 mcg/w: 1 (%6)	20 mcg/w: 1 (%6,25)	30 mcg/w: 1 (%14,28)
	50 mcg/w: 2 (%11,7)	40 mcg/w: 1 (%6,25)	40 mcg/w: 1 (%14,28)
	60 mcg/w: 1 (%6)	50 mcg/w: 1 (%6,25)	50 mcg/w: 2 (%28,57)
		60 mcg/w: 2(%12,5)	60 mcg/w: 2 (%28,57)
	Total: 4 (%23,52)	Total: 5 (%31,25)	Total: 6 (%85,71)
	Average Dose Used: 50 mcg/w	Average Dose Used: 46 mcg/w	Average Dose Used: 48,33 mcg/w

HT: Hypertension DM: Diabetes Mellitus EPO: Erythropoietin

Table 3. Laboratory Values of Total, Patient Group and Control Group

	Total	Patient	Control	P
	Mean±SD or Median Value (Min. – Max.)	Mean±SD or Median Value (Min. – Max.)	Mean±SD or Median Value (Min. – Max.)	
WBC (10^3µ/L)	8.31±2.92	8.99±3.25	6.90±1.19	0.003
Hemoglobin (g/dL)	10.75±2.52 (7.5-16.8)	9.14±0.63 (7.5-9.9)	14.14±1.32 (12.1-16.8)	<0.001
MCV (fL)	85.13±8.07	85.55±877	84.25±6.52	0.501
Platelets (10^3µ/L)	261.39±94.19	272.35±101.25	238.32±74.44	0.212
BUN (mg/dL)	35.25±19.75	44.67±17.04	15.42±3.88	<0.001
Creatinine (mg/dL)	1.92±1.25	2.46±1.19	0.79±0.14	<0.001
eGFH (ml/min/1,73m^2)	35.94 (7.0-104.21)	27.97 (7-59.89)	94.90 (72.41-104.21)	<0.001
Sodium (mmol/L)	138.02± 3.46	137.10± 3.51	139.5± 2.48	0.004
Potassium (mmol/L)	4.58±0.52	4.69±0.57	4.37±0.34	0.010
Calcium (mg/dL)	9.24±0.68	9.07±0.74	9.62±0.37	0.002
Phosphorus (mg/dL)	3.97±0.89	4.25±0.91	3.40±0.51	<0.001
PTH (pg/dL)	102.0 (16.7-845.0)	125.50 (16.7-845.0)	50.6 (18.3-174.0)	<0.001
ALP(U/L)	103.03±53.91	111.53±61.77	85.16±24.48	0.144
AST (U/L)	21.17±9.76	21.35±10.57	20.79±8.06	0.782
ALT (U/L)	18.19±7.79	17.30±7.78	20.05±7.70	0.146
Uric acid (mg/dL)	6.56±2.33 (2.7-14.7)	7.13±2.42 (2.7-14.7)	5.38±1.63 (2.9-10.1)	0.005
Albumin(g/dL)	4.80±0.57	3.82±0.59	4.43±0.24	<0.001
Ferritin(ng/mL)	63.50	74.75	37.50	0.050
Vitamin B12 (Pg/Ml)	506.81±472.17	583.80±556.12	344.74±86.02	0.330
Folate (ng/mL)	8.90±4.15	7.75±3.91	11.33±3.63	<0.001
CRP (mg/L)	7.25±5.24	8.14±5.61	5.38±3.83	0.024
LincRNA-EPS Expression	0.27 (0.10-0.99)	0.5255 (0.000017-12.99)	0.000041 (0.00000013-0.25)	<0.001

WBC: White Blood Cell Count, MCV: Mean Corpuscular Volume, BUN: Blood Urea Nitrogen, eGFR: Estimated Glomerular Filtration Rate, PTH: Parathormone, ALP: Alkaline Phosphatase, AST: Aspart Aminotransferase, ALT: Alanine Aminotransferase, CRP: C-Reactive Protein

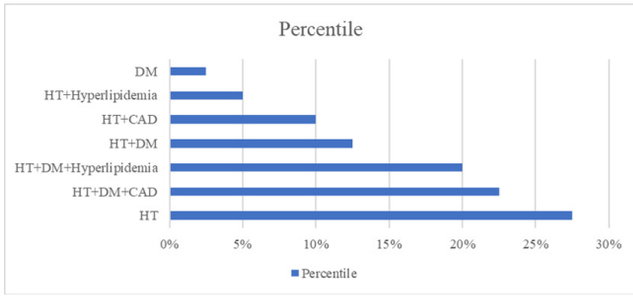

Figure 1. Distribution of Additional Diseases to CKD in the Patient Group
DM: Diabetes Mellitus HT: Hypertension CAD: Coronary Artery Disease

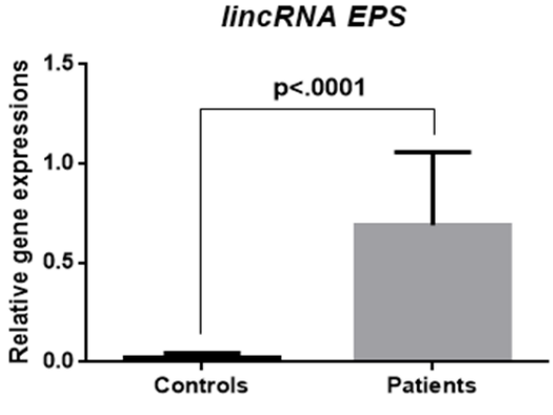

Figure 2. LincRNA-EPS Expression Levels in Patient and Control Groups

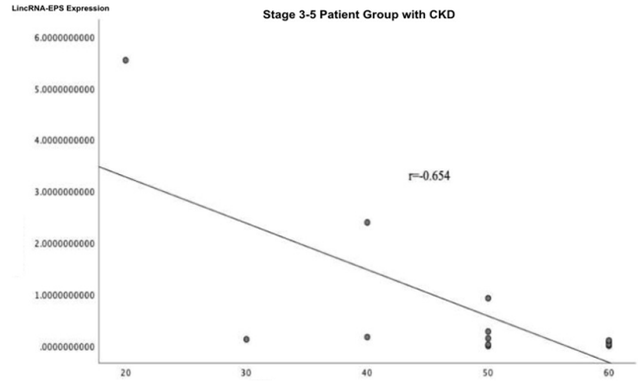

Figure 3. Negative Correlation Between EPO Levels and LincRNA-EPS Expression Levels in the Patient Group

patients with CKD and the healthy control group are given in Table 3. Median and quartile lincRNA-EPS expression values in the healthy control group: The median value was 0.000041; 1st quartile (Q1): 0.000017, 2nd quartile (Q2): 0.000041, 3rd quartile (Q3): 0.00038; in the patient group: The median value was 0.5255; 1st quartile (Q1): 0.0072, 2nd quartile (Q2): 0.5255, 3rd quartile (Q3): 0.00038. Considering these data, lincRNA-EPS expression values were found to be significantly higher in the CKD group (p <0.001) (Figure 2). In the patient group, there was no statistically significant relationship between lincRNA-EPS expression levels in patients who received and did not receive EPO (p=0.106). There was no statistically significant correlation between lincRNA-EPS expression levels between diabetic and non-diabetic patients in the patient group (p=0.438).

Correlation Analysis Results

A statistically significant negative correlation was found

between EPO levels and lincRNA-EPS expression levels in the patient group (r=-0.654, p=0.011) (Figure 3). There was no statistically significant correlation between the eGFR level of the patients and the lincRNA-EPS expression levels (p=0.897). Statistically significant positive correlation was found between eGFR values and hemoglobin levels in the patient group (r= 0.321, p=0.043). A statistically significant negative correlation was found between eGFR values and the number of patients using EPO in the patient group (r=-0.432, p=0.005) and statistically significant positive correlation was found between the CKD stages of the patients and the number of patients using EPO (r= 0.377, p=0.016). In demographic data, no statistically significant correlation was found between age, BMI, and lincRNA-EPS expression levels in both the patient group and the healthy group (p=0.458, p=0.650 and p=0.580, p=0.814).

Discussion

This is the first report examining the lincRNA_EPS expression levels in CKD patients with renal anemia. We indicated the lincRNA-EPS expression values were found to be significantly higher in the CKD group (p <0.001). There was no statistically significant correlation between the eGFR level of the patients and the lincRNA-EPS expression levels (p=0.897). However, statistically significant positive correlation was found between eGFR values and hemoglobin levels in the patient group (r= 0.321, p=0.043). Moreover, in the patient group, there was no statistically significant relationship between lincRNA-EPS expression levels in patients who received and did not receive EPO (p=0.106). There was no statistically significant correlation between lincRNA-EPS expression levels between diabetic and non-diabetic patients in the patient group (p=0.438).

The worldwide prevalence of CKD is estimated to be 8-16% and this number continues to rise [22]. It is important to manage complications related to pathologies such as anemia, mineral and bone disorders, hydroelectrolytic disorders, metabolic acidosis and cardiovascular disease in patients diagnosed with CKD [23].

Studies have found an increased risk of developing or deepening anemia in correlation with the increase in CKD stage and the decrease in eGFR. In addition, evaluation of the patients after 5 years of follow-up studies data showed that CKD patients with anemia at baseline had a greater loss of renal function and a greater increase in all cardiovascular risks (myocardial infarction, heart failure, stroke, or death) [24]. In this study, a statistically significant positive correlation was shown between the decrease in eGFR and the decrease in hemoglobin levels. Increased apoptosis of RBC progenitors can be associated with a variety of anaemias, including inflammation and cancer-related conditions. It is possible that pharmacological inhibition of proapoptotic signaling pathways may be clinically beneficial, especially since many of these anemias are resistant to EPO therapy [25]. We investigated whether there is a significant relationship and correlation between lincRNA-EPS expression levels, renal anemia and EPO usage in stage 3-5 CKD patients. This study is the first in the literature to analyze this relationship. Considering that most of the lncRNA studies are carried out in animal experiments, it is particular important because the data obtained human origin in this study.

As a result of our study, statistically significant increase was found in lncRNA-EPS expression in the CKD patient group compared to the healthy control group. In addition, it was observed that there was significant negative correlation between the amount of EPO usage and the expression of lincRNA-EPS in the correlation analysis performed within the patient group. As a result of these data we have obtained, it is possible to establish a link between renal anemia, lincRNA-EPS and EPO usage. In patients with CKD, renal anemia deepens as a result of the decrease in the amount and/or effect of EPO, which protects erythroid precursors from apoptosis, and accelerates the progression of erythroid precursors to apoptosis. Considering the increased lincRNA-EPS expression level and the inverse correlation between EPO usage and lincRNA-EPS expression level in CKD patients with renal anemia; in order to facilitate erythropoiesis, the increase in lincRNA-EPS expression level and suppression of Pycard which is a proapoptotic gene, seems to be a possible mechanism.

Limitations of the study

The limitations of our study include the fact that our study is a single-center and cross-sectional study, making it difficult to determine any causal relationship, and the decrease in the number of patients who meet our study group criteria due to the Covid-19 outbreak.

Conclusion

In conclusion, larger and more clinical studies are needed to fully elucidate the mechanism of action of the renal anemia-EPO-lincRNA-EPS relationship revealed by us. In the light of these studies, it will be possible to identify new factors that play a role in the formation mechanisms of renal anemia and to evaluate new treatment alternatives. In this way, it will be possible to prevent the emergence of many bad clinical conditions accompanying renal anemia such as increased cardiovascular risk, increased rate of renal function loss as well as clinical conditions directly caused by anemia such as low quality of life, increased transfusion need, early and with less cost.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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